Human iPSC-Derived Cerebral Organoids Model Cellular Features of Lissencephaly and Reveal Prolonged Mitosis of Outer Radial Glia.

Journal: Cell Stem Cell

Publication Year: 2017

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PubMed link: 28111201

Funding Grants: Center of Excellence for Stem Cell Genomics - Stanford

Public Summary:

Scientific Abstract:
Classical lissencephaly is a genetic neurological disorder associated with mental retardation and intractable epilepsy, and Miller-Dieker syndrome (MDS) is the most severe form of the disease. In this study, to investigate the effects of MDS on human progenitor subtypes that control neuronal output and influence brain topology, we analyzed cerebral organoids derived from control and MDS-induced pluripotent stem cells (iPSCs) using time-lapse imaging, immunostaining, and single-cell RNA sequencing. We saw a cell migration defect that was rescued when we corrected the MDS causative chromosomal deletion and severe apoptosis of the founder neuroepithelial stem cells, accompanied by increased horizontal cell divisions. We also identified a mitotic defect in outer radial glia, a progenitor subtype that is largely absent from lissencephalic rodents but critical for human neocortical expansion. Our study, therefore, deepens our understanding of MDS cellular pathogenesis and highlights the broad utility of cerebral organoids for modeling human neurodevelopmental disorders.